

A DRUG NAME: DOXORUBICIN**SYNONYM(S):** Hydroxyl daunorubicin, Dox, Adria**COMMON TRADE NAME(S):** Adriamycin®, Adriamycin PFS®, Adriamycin RDF® (Pharmacia & Upjohn), Doxorubicin (Faulding, Novopharm)**B MECHANISM OF ACTION AND PHARMACOKINETICS**

Daunorubicin and its 14-hydroxy derivative, doxorubicin, are anthracycline antibiotics produced by the fungus *streptomyces peucetius*. Doxorubicin damages DNA by intercalation of the anthracycline portion, metal ion chelation, or by generation of free radicals. Doxorubicin has also been shown to inhibit DNA topoisomerase II which is critical to DNA function. Cytotoxic activity is cell cycle phase-nonspecific.

Oral Absorption	no (5%)	
Distribution	highest concentrations in liver, spleen, kidney, heart, small intestines, lung; crosses placenta; found in breast milk	
	cross blood brain barrier?	Does not cross blood brain barrier
	Vd	25 L/kg
	PPB	79-85%
Metabolism	liver (major site) and other tissues; elimination primarily via liver and biliary system	
	active metabolite(s)	doxorubicinol (major metabolite)
	inactive metabolite(s)	yes
Excretion	predominantly in bile, 40-50% in feces within 7 days	
	urine	4-5% over 5 days
	t $\frac{1}{2}$ α	12 minutes
	t $\frac{1}{2}$ β	3.3 hours
	t $\frac{1}{2}$ γ	29.6 hours
	Cl	17+3 mL/min/kg 503 mL/min/m ² (↑ in children)

C INDICATIONS AND STATUS

- * Acute lymphocytic leukemia
- * Acute myeloblastic leukemia
- * Bladder cancer
- * Breast cancer
- * Endometrial cancer
- * Gastric cancer
- * Head and neck cancer, squamous cell
- * Hodgkin's disease
- * Lung cancer, non-small cells
- * Neuroblastoma
- * Non-Hodgkin's lymphoma
- * Osteogenic sarcoma
- * Ovarian cancer
- * Sarcoma, soft tissue
- * Testicular cancer
- * Thyroid cancer
- * Wilms' tumour
- * Therapeutic Products Programme, Health Canada approved indication

Other uses include:
 Adrenocortical cancer
 Carcinoid syndrome (small bowel)
 Ewing's sarcoma
 Gynecological sarcoma
 Hepatic cancer
 Islet cell cancer
 Multiple myeloma
 Pancreatic cancer
 Prostate cancer
 Retinoblastoma
 Rhabdomyosarcoma

D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT	ONSET	
cardiovascular	transient arrhythmias (41%)	I	
	<u>congestive heart failure</u> cumulative dose = (<550 mg/m ²)(0.1-1.2%) (>550 mg/m ²)(30%)	D	L
	<u>cardiomyopathy</u> (0.4-9% dose related)	D	L
dermatologic	facial flushing with rapid injection	I	
	radiation recall reaction (rare)	I	
	alopecia (complete in most patients)	E	
	hyperpigmentation of fingers (in children, rare)	D	
	nail changes	D	
extravasation hazard (refer to Appendix 2)	VESICANT , local necrosis	I	

D ADVERSE EFFECTS Continued

ORGAN SITE	SIDE EFFECT	ONSET
gastrointestinal	nausea and vomiting (frequent, may be severe) (onset 3-4 hours, duration 6-12 hours)	I
	Diarrhea ; typhilitis	E I
	Mucositis (stomatitis, esophagitis) (may occur 5-10 days after)	E
hematologic	Myelosuppression (primarily leukocytes), nadir 6-13 days, recovery in 21-24 days	E
	Secondary leukemia	L
hypersensitivity	Type I (anaphylactic), (rare)	I
	skin rash, fever, chills	E
injection site	doxorubicin flare (histamine release)	I
	pain on injection	I
	chemical phlebitis	I
ocular	conjunctivitis (rare)	E
renal/metabolic	red colouration of urine for 1-2 days	I
	hyperuricemia (during periods of active cell lysis)	I
reproductive	infertility	L

Dose-limiting side effects are underlined.

I = immediate (onset in hours to days); E = early (days to weeks);

D = delayed (weeks to months); L = late (months to years)

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (eg, some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

Cardiotoxicity can be divided into an initial acute effect with transient electrocardiographic abnormalities, reported in up to 41% of patients; and a later cumulative, dose-dependent cardiomyopathy. The acute electrocardiographic changes are usually reversible, unrelated to total dose, return to baseline readings within a few days to two months and usually are not an indication to discontinue the doxorubicin. The more serious cardiotoxicity is a dose-dependent cardiomyopathy (0.4-9% of all patients), which has an attendant mortality as high as 61%. Risk factors include total dose, schedule, increased age, pre-existing cardiac disease, prior mediastinal radiotherapy and other antineoplastic drugs. The onset of cardiomyopathy may be delayed, occurring 6 months or more after therapy.

D

ADVERSE EFFECTS Continued

The incidence of drug-induced congestive heart failure ranges from 0.1-1.2% with cumulative dose of $<550 \text{ mg/m}^2$ in contrast to 30% incidence with cumulative dose $>550 \text{ mg/m}^2$. For a graphic estimate of the cumulative probability of developing doxorubicin-induced congestive heart failure (CHF) in adults versus total cumulative dose see Von Hoff 1979. Certain patients (prior mediastinal radiation, prior anthracyclines, older age, hypertension) are at higher risk and may develop cardiotoxicity at lower cumulative doses of doxorubicin and should receive cumulative doses of doxorubicin $<400 \text{ mg/m}^2$. In adults with risk factors cardiac function monitoring (echocardiogram or MUGA scan) should be performed before treatment and periodically throughout treatment. All patients who have received total cumulative doses of 450 mg/m^2 and in whom further therapy with doxorubicin is indicated should undergo cardiac assessment before continuing treatment.

It has been observed that children less than 15 years of age are more likely to develop CHF from cumulative doses greater than 550 mg/m^2 than those patients aged 15 to 40 years. In children, clinical cardiotoxicity increases rapidly at a cumulative dose of about 450 mg/m^2 , but individual patients may have a lower threshold and develop toxicity at a significantly lower dose. Cardiac dysfunction may appear several months to years after anthracycline therapy, therefore monitoring should continue after therapy is complete. For children receiving anthracyclines, the Cardiology Committee of the Children's Cancer Group recommends the following monitoring of cardiac function:

1. Echocardiogram [echo] (or radionucleotide angiocardigraphy [RNA]) as baseline.
2. Echo before every other subsequent course of anthracycline when the cumulative dose is $<300 \text{ mg/m}^2$.
3. Echo (or RNA) before each course of anthracycline when the total cumulative dose $>300 \text{ mg/m}^2$ plus mediastinal radiation $>1000 \text{ rads}$.
4. Echo and RNA before each course of anthracycline when the total course is $\geq 400 \text{ mg/m}^2$.

Erythematous streaking (a histamine release phenomena) along the vein proximal to the site of injection has been reported, and must be differentiated from an extravasation event. This '*doxorubicin flare*' reaction usually subsides within 30 minutes. The injection may be continued, more slowly in the same site or may be changed to another site. Diphenhydramine 25 mg (1 mg/kg/dose in children), or hydrocortisone 100 mg (1 mg/kg/dose in children), by slow IV push over 5 minutes into the IV line may hasten clearing of the reaction.

The *tissue necrosis* that occurs with *extravasation* may happen days to weeks after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected.

Doxorubicin has the potential to enhance radiation injury to tissues. While often called '*radiation recall reactions*', the timing of the radiation may be before, concurrent with or even after the administration of the doxorubicin. The skin is the site most commonly affected, resulting in erythema followed by dry desquamation. Skin reactions generally occur only if the drug is given within 7 days of the radiation. Rarely, reactions after 30 days have been noted. Skin involvement, while unpleasant, is not as debilitating as is the case for internal organs. Enhancement of radiation injury to the esophagus and gastrointestinal tract is most severe when the drug and the radiation are given concomitantly. Recurrent injury to a previously irradiated site may occur weeks to months following radiation.

E

DOSING

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Adults:**Intravenous:**

q1-2w: 10-30 mg/m² bolus
 q3-4w: 60-90 mg/m² bolus
 q3-4w: 20-30 mg/m²/day bolus for 3 consecutive days
 q3w: 60-75 mg/m² 10 hour infusion
 q3-4w: 60-90 mg/m² 24-96 hour infusion

Intra-arterial:**Intravesical:**

q3-4w: 25 mg/m²/day for 3 consecutive days
 q1w: 50-80 mg via bladder instillation, retained 1-2 hours, weekly x 4 then monthly

Maximum lifetime dose:

550 mg/m² (normal cardiac function)
 400 mg/m² (in combination with thoracic radiation or cyclophosphamide, or in patients with cardiac risk factors)
 Careful cardiac monitoring is important, as cardiotoxicity may occasionally occur at lower cumulative doses. If tumour responding when lifetime dose reached, obtain cardiac consultation before continuing treatment.

Dosage in myelosuppression:

modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure:**Dosage in hepatic failure:**

Bilirubin (μmol/L)	% usual dose
1-2x ULN	50%
2-4x ULN	25%
>4x ULN	0%

Dosage with ascites:

use ideal body weight for body surface area calculations.

Children:

q3-8w: 45-75 mg/m² IV
 20-30 mg/m²/day x 3 days IV

F

ADMINISTRATION GUIDELINES

- Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline or 2/3:1/3 Give 2 to 4mg (1-2ml) per minute
- Doses ≤100mg may be mixed in 50mL minibag (5% Dextrose), doses >100mg may be mixed in 100mL minibag (5% Dextrose); Infuse through sidearm of free flowing IV over 10-30 minutes
- Slow down injection rate if erythematous streaking occurs
- PROTECT FROM LIGHT

G SPECIAL PRECAUTIONS

Cardiac toxicity is cumulative across members of the anthracycline (doxorubicin, epirubicin, daunorubicin, idarubicin and anthracenedione (mitoxantrone) class of drugs). Patients who have received these agents are at increased risk of toxicity, and should be carefully monitored. The cumulative doses resulting in cardiotoxicity are lower in patients who have received radiation to the mediastinal area of concomitant therapy with other cardiotoxic agents such as cyclophosphamide.

Contraindicated in patients with severe cardiovascular disease, unstable conditions including hypertension, angina and arrhythmias; and in patients with hyperbilirubinemia.

Doxorubicin has been shown to have mutagenic *and carcinogenic properties* in experimental models. Its safe use in *pregnancy* and its effects on fertility have not been established. Present in *breast milk*, therefore breast feeding is not recommended.

H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
barbiturates	therapeutic effects of doxorubicin decreased	Increased plasma clearance of doxorubicin	monitor if barbiturates initiated or discontinued
cyclophosphamide	exacerbation of cyclophosphamide induced hemorrhagic cystitis	uncertain	caution
cyclophosphamide	increased risk potential for cardiotoxicity	uncertain	monitor, may need to modify dose of doxorubicin
digoxin	decreased digoxin levels; interaction may occur several days after treatment	decreased digoxin absorption	monitor digoxin levels and patient
mercaptopurine	enhanced hepatotoxicity	uncertain	monitor
quinolones	antimicrobial effect of quinolones decreased	decreased quinolones absorption	monitor, may need to modify dose of quinolones
cytarabine	Typhlitis	uncertain, treat appropriately	
streptozocin	increased toxicity of doxorubicin	Liver damage by streptozocin decreases metabolism of doxorubicin	caution

RECOMMENDED CLINICAL MONITORING

Recommended Clinical Monitoring

- Clinical exam for symptoms of CHF
- Periodic cardiac tests for all patients with cardiac risk factors or patients at or above the threshold dose levels
- Baseline liver function tests (esp. If poor P.S.)

■ CARDIAC

*At cumulative dose threshold
and subsequent intervals*

0. None
1. —
2. Asymptomatic, resting ejection fraction decline by >10% baseline; or abnormal cardiac function tests (LVEF>50) with no baseline for comparison
3. Mild Congestive Heart Failure, responds to therapy
4. Severe/refractory Congestive Heart Failure

For Cardiac Toxicity Ratings:

First rating at the Doxorubicin cumulative dose threshold of 450mg/m^2 , & repeat ratings at each cumulative dose increment of 100mg/m^2 above threshold (Cumulative dose sooner for high risk patients, eg. pre-existing cardiac disease, prior chest irradiation)

Note: Threshold Cumulative dose reduced proportionately if other anthracycline or anthracenedione drugs have been given; cardiotoxicity is additive.

Suggested Clinical Monitoring

- Baseline cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors